UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,235	02/20/2001	Hicham Moulay Alaoui Ismaili	PHARMA-115	4355

24999 7590 07/02/2003

MILLEN, WHITE, ZELANO & BRANIGAN, PC
2200 CLARENDON BLVD
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	13

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/785,235	Applicant(s) ISMAILI ET AL.	
	Examiner Patrick T. Lewis	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of species A1 (method for treating Hepatitis C) and species B2 (wherein group **B** is a pyrimidine or an analogue thereof) in Paper No. 9 dated October 23, 2002 is acknowledged.

Objections/Rejections Set For the in Office Action dated December 30, 2002

2. Claim 1 was objected to because of the following informalities: In line 3, the examiner suggests incorporating language indicating to whom the therapeutic composition is administered. The examiner suggests adding the phrase "to a host in need thereof," after the term "effective amount". In line 16 the term "are" should be replaced with the term "is". Appropriate correction is required.

3. Claims 1-18 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the term "analogue" renders the instant claim and all subsequent depending claims in which the variable **B** is not clearly defined indefinite. Applicant has failed to particularly point out the modifications to the pyrimidine moiety which distinctly set forth the structural core modifications or chemical moieties effectuating derivatization. In the absence of distinct modifications or derivatizing moieties, the term "analogue" is indefinite in all occurrences.

In claim 1, the alternative manner in which applicant defines variables represented by **Ra** renders the instant claim and all subsequent depending claims in which the variable **Ra** has not been clearly defined indefinite. It is unclear whether the terms appearing after the phrase "carbonyl substituted with a C_{1-6} alkyl" are intended to represent moieties attached to the carbonyl or if said terms represent moieties attached directly to the oxygen atom.

In claim 1, variables $\mathbf{D_1}$ and $\mathbf{D_2}$ have not been clearly defined. The phrase "can also be" renders the instant claim and all subsequent depending claims in which variables $\mathbf{D_1}$ and $\mathbf{D_2}$ have not been clearly defined indefinite. The phrase "can also be joined" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "can also be joined"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

In claims 12 and 13, the parenthetical phrase "(ribarivin base)" renders the claim indefinite because it is unclear whether the limitation(s) enclosed in parentheses are part of the claimed invention. See MPEP § 2173.05(d).

Claim 14 recites the limitation "according to claim 1 wherein the compound of formula I is chosen" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

4. Claims 1, 2, 4, 6, 10, 12, and 15-16 were rejected under 35 U.S.C. 102(e) as being anticipated by Tan et al. WO 00/50064 (Tan).

Tan discloses a method for treating flavivirus or rhabdovirus infection comprising administering to the host an interferon and nucleoside of formula (I) wherein –**X**- is =CH-

, -CH2-, or –O-; **Nu** is selected from the group consisting of purines, pyrimidines, and five- or six-member aglycones; $\mathbf{R_2}$ and $\mathbf{R_3}$ are independently selected from the group consisting of H, OH, O-acyl, O-aryl, and O-silyl; and $\mathbf{R_1}$ is as defined for $\mathbf{R_2}$ and $\mathbf{R_3}$ or is O-phosphate (Page 2, lines 6-25). Specific compounds disclosed by Tan, which read on the instantly claimed method of the treatment include 3-deazauridine and 6-azauridine (Page 14, Table 1). The flavivirus maybe yellow fever virus, kunjin virus, dengue virus, hepatitis C virus, or an encephalitis virus (page 17, lines 16-20). The interferon may be an interferon α, such as interferon $\alpha 2$ or $\alpha 8$, or interferon β (Page 5, lines 27-30). Thus, Tan et al anticipated the instantly claimed invention.

5. Claims 1-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Tan et al. WO 00/50064 (Tan), Johansson et al. U.S. Patent 5,506,215 (Johansson), and Hamedi-Sangsari et al. U.S. Patent 5,705,522 (Hamedi).

Claims 1-18 are drawn method of treating a hepatitis C infection in a host comprising administering a therapeutically effective amount of a compound of formula (Ib) or a pharmaceutically acceptable salt thereof. Claims 2 and 14-15 depend from claim 1. Claim 2 limits **Z** to OH. Claim 14 limits formula (I) to one of Compounds 1-54. Claim 15 is drawn to a method wherein said compound is used in combination with at least one further therapeutic agent. Claims 3-6, 10, 12, and 16 depend from claim 2. Claim 3 limits $\mathbf{D_1}$ to H and $\mathbf{D_2}$ to F. Claims 4-6 limit **Ra** to H, monophosphate, diphosphate, and triphosphate; triphosphate; and H, respectively. Claims 10 and 12 limit **B**. Claim 16 is drawn to a method wherein said compound is used in combination with at least one further therapeutic agent. Claims 7-9, 11, 13, and 17 depend from

claim 3. Claims 7-9 limit **Ra** to H, monophosphate, diphosphate, and triphosphate; triphosphate; and H, respectively. Claims 11 and 13 limits **B**. Claim 17 is drawn to a method wherein said compound is used in combination with at least one further therapeutic agent.

Tan teaches a method for treating flavivirus or rhabdovirus infection comprising administering to the host an interferon and nucleoside of formula (I) wherein –**X**- is =CH- , -CH2-, or –O-; **Nu** is selected from the group consisting of purines, pyrimidines, and five- or six-member aglycones; $\mathbf{R_2}$ and $\mathbf{R_3}$ are independently selected from the group consisting of H, OH, O-acyl, O-aryl, and O-silyl; and $\mathbf{R_1}$ is as defined for $\mathbf{R_2}$ and $\mathbf{R_3}$ or is O-phosphate (Page 2, lines 6-25). Specific compounds taught by Tan, which overlap with the instantly claimed compounds of the treatment method include 3-deazauridine and 6-azauridine (Page 14, Table 1). The flavivirus maybe yellow fever virus, kunjin virus, dengue virus, hepatitis C virus, or an encephalitis virus (page 17, lines 16-20). The interferon may be an interferon α, such as interferon α2 or α8, or interferon β (Page 5, lines 27-30).

Tan differs from the instantly claimed invention in that Tan: 1) does not teach $\mathbf{R_2}$ [$\mathbf{D_2}$] as being F; 2) does not teach explicitly teach $\mathbf{R_1}$ as being triphosphate but rather teaches O-phosphates in general; and 3) does not teach the specific embodiments of formula (I) described in claim 14. These deficiencies, however, would have been obvious to the skilled artisan in view of the teachings of Johansson and Hamedi.

Johansson teaches analogous pyrimidine nucleosides of formula (I) useful for the treatment of infections caused by retroviruses and hepatitis B virus in mammals and

man wherein R^6 [D_2] is F (column 4, lines 50-55; column 3, line 45 through column 4, line 49). Johansson further teaches the compounds of formula (I) cooperate synergistically or additively with a wide range of other therapeutic agents, thereby enhancing the therapeutic potential of both agents with adding the toxic effects, thus increasing the therapeutic ratio (column 8, lines 42-46).

Hamedi teaches the use of analogous nucleosides (AZT, ddC, ddA, ddG, ddI, ddT, 3TC, and d4T) useful for treating both hepatitis B and hepatitis C viruses (column 3, lines 22-54).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Tan, Johansson, and Hamedi in order to treat patients suffering from hepatitis C with the instantly disclosed nucleoside derivatives. A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979).

Applicant's Response dated April 23, 2003

6. In the Response filed April 23, 2003, claims 1, 2, 4, 7, and 10-18 were amended and claims 19-40 were added. Applicant presented arguments directed to the rejection of claims 1-18 under 35 U.S.C. 112, second paragraph; the rejection of claims 1, 2, 4, 6,

10, 12, 15, and 16 under 35 U.S.C. 102(e); and the rejection of claims 1-18 under 35 U.S.C. 103(a). Claims 1-40 are pending. An action on the merits of claims 1-40 is contained herein below.

7. The rejection of claims 1-18 under 35 U.S.C. 112, second paragraph is maintained for the reasons of record as set forth in the Office Action dated December 30, 2002.

8. Applicant's arguments with respect to claims 1, 2, 4, 6, 10, 12, 15, and 16 under 35 U.S.C. 102(e) and claims 1-18 under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Response to Arguments

9. Applicant's arguments filed April 23, 2003 have been fully considered but they are not persuasive.

In regards to the term "analogue", all claims wherein the variable B is defined as an "analogue" are indefinite in all occurrences. Applicant has directed the examiner's attention to page 27 of the instant disclosure wherein "analogues" are described as "...a purine or pyrimidine base found in nucleotide or an analogue thereof which mimics such bases in that their structures (the kinds of atoms and their arrangement) are similar to the normal bases but may possess additional or lack certain of the functional properties of the normal bases." Although claims are interpreted in light of the specification, limitations from the specification are not read into the claims. Furthermore, the term is not seen to be limited. Page 27 of the disclosure merely points out "analogues" which

may read upon the variable **B**. If it is applicant's intention to have the invention limited to analogs described of page 27 of the specification (i.e. those derived by replacement of CH moiety by a nitrogen atom, etc.), the claims should be amended to include such limitation(s).

In regards to the variable **Ra**, it appears that applicant has missed the point of the rejection. Applicant has listed a number of moieties representative of the variable **Ra**. Commas separate the members of the list. Simply separating everything in this list by commas renders the claim(s) indefinite as it is unclear if **Ra**, for example, represents: 1) carbonyl substituted by a straight chain, branched chain or cyclic C_{1-6} alkyl which is unsubstituted or substituted...; or 2) (a) carbonyl substituted by a straight chain, (b) branched chain, or (c) cyclic C_{1-6} alkyl which is unsubstituted or substituted. If it is applicant's intention for **Ra** to represent, for example, a carbonyl substituted by a branched chain, the claims should be amended to more clearly reflect applicant's intentions. The examiner suggests the use of semicolons.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 32 and 33 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is unclear. The phrase "said compound and said further therapeutic agent are sequentially" renders the claim indefinite. Without clarification, one of ordinary skill in the art cannot determine the metes and bounds of the invention.

Claim 33 is unclear. The phrase "said compound and said further therapeutic agent are simultaneously in separate or combined pharmaceutical formulations" renders the claim indefinite.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 1-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mikhailopulo et al. *J. Med. Chem.* (1991), Vol. 34, pages 2195-2202 (Mikhailopulo), Brillanti et al. *Ital. J. Gastroenterol Hepatol (1999), Vol. 31, pages 130-134 (Brillanti),* and Matthes et al. U.S. Patent 4,963,662 (Matthes).

Claims 1-40 are drawn method of treating or preventing a hepatitis C infection in a host comprising administering a therapeutically effective amount of a compound of formula (Ib) or a pharmaceutically acceptable salt thereof. Claims 14, 19, and 34 depend from claim 1. Claim 14 limits formula (I) to a specific compound. Claim 19 is limited to a method of treatment. Claim 34 is drawn to a method wherein the host is human. Claims 2, 15, 20-25, 27-30, and 35 depend from claim 19. Claim 2 limits **Z** to OH. Claim 15 is drawn to a method further comprising administering a further therapeutic agent. Claim 20 limits **Ra** and **Rb**. Claims 20-25 limit **B**. Claim 27 limits **Z**. Claim 28 limits $\mathbf{D_1}$ and $\mathbf{D_2}$. Claims 29-30 limit the amount of compound administered. Claim 35 is drawn to a method wherein the host is human. Claims 3-6, 10, 12, 16, and 36 depend from claim 2. Claim 3 limits $\mathbf{D_1}$ to H and $\mathbf{D_2}$ to F. Claims 4-6 limit **Ra**. Claims 10 and 12 limit **B**. Claim 16 is drawn to a method further comprising

administering a further therapeutic agent. Claim 36 is drawn to a method wherein the host is human. Claims 7-9, 13, 17, and 37 depend from claim 3. Claims 7-9 limit **Ra**. Claim 13 limits **B**. Claim 17 is drawn to a method further comprising administering a further therapeutic agent. Claim 37 is drawn to a method wherein the host is human. Claims 18 and 38 depend from claim 14. Claim 18 is drawn to a method further comprising administering a further therapeutic agent. Claim 38 is drawn to a method wherein the host is human. Claim 26 depends form claim 25 and further limits variable **B**. Claim 31 depends from claim 15. Claim 31 drawn to a method wherein the formulation further comprises a pharmaceutically acceptable carrier. Claims 32-33 depend from claim 31. Claims 32-33 limit how the compound and additional therapeutic agent are administered. Claims 39-40 are drawn method of treating or preventing a hepatitis C infection in a host comprising administering a therapeutically effective amount of a compound of formula (Ib) or a pharmaceutically acceptable salt thereof wherein said method does not include administration of an interferon. Claim 40 depends from claim 39 and limits the host to a human.

Mikhailopulo teaches antiviral activity of 3'-deoxy-3'-fluoro analogues of ribonucleosides against (±)DNA viruses, (+)RNA viruses (HCV is a positive-stranded RNA virus belonging to the *Flaviviridae* family), and (±)RNA viruses (page 2200, column 1, paragraph 2). The ribonucleoside analogues taught by Mikhailopulo as having antiviral activity are within the scope of applicant's formula (Ib). Mikhailopulo specifically teaches the use of compounds **23**, **25**, **26** and **27** (page 2196, column 2, Scheme 2). Compound **23** reads upon formula (Ib) wherein: **Ra** = H; **B** = uracil-1-yl; **Z** = OH; $\mathbf{D_1}$ = F;

and D_2 = H. Compound **25** reads upon formula (Ib) wherein: **Ra** = H; **B** = cytosin-1-yl; **Z** = OH; D_1 = F; and D_2 = H. Compound **26** reads upon formula (Ib) wherein: **Ra** = H; **B** = adenin-9-yl; **Z** = OH; D_1 = F; and D_2 = H. Compound **27** reads upon formula (Ib) wherein: **Ra** = H; **B** = guanin-9-yl; **Z** = OH; D_1 = F; and D_2 = H. Mikhailopulo further teaches that the analogues have biological activity following intracellular conversion to 5'-triphosphates (page 2195, column 1, paragraph 1).

Mikhailopulo differs from the instantly claimed invention in that Mikhailopulo: 1) does not explicitly teach treatment of HCV; 2) does not teach the administration of a further therapeutic agent; and 3) does not teach a dosage regimen. The deficiencies of Mikhailopulo however would have been obvious to one of ordinary skill in the art at the time of the invention when viewed in light of the teachings of Brillanti and Matthes.

Brillanti teaches that interferon alpha (IFNα) is the therapy of choice for chronic hepatitis C (page 130, paragraph 1). Brillanti further teaches treatment with triple antiviral combination therapy (IFNα + ribavirin + amantadine) (page 130, column 2, paragraph 3).

Matthes teaches treatment of Rauscher murine leukemia virus with compounds within the scope of formula (Ib) (Abstract; column 6, lines 16-56). Matthes teaches the administration of 69 mg/kg/day of FTdR in the treatment regimen.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat patients suffering from HCV with compound **23**, **25**, **26**, **27**, or their 5'-triphosphates of Mikhailopulo. Although Mikhailopulo does not explicitly teach the treatment of HCV, one of ordinary skill in the art at the time of the invention would have

a reasonable expectation of success in treating HCV (positive-stranded RNA virus) since Mikhailopulo teaches the antiviral activity of viruses of this type. It would have also been obvious to use a combination therapy (ribonucleoside of Mikhailopulo + IFNα) for the treatment of HCV. It is generally considered prima facie obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. As shown by the recited teachings, the instant claims define nothing more than the concomitant use of two conventional anti-inflammatory agents. It would follow that the recited claims define prima facie obvious subject matter. *Ex part Quadranti* (BdPatApp&Int) 25 USPQ2d 1071. Determining the active ingredient dosage level required to effect optimal therapeutic benefit is well within the skilled artisan's purview and the benefits of achieving such maximization obvious, to said skilled artisan.

Conclusion

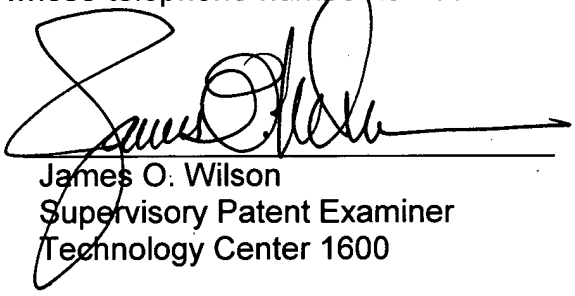
16. Claims 1-40 are pending. Claims 1-40 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Patrick T. Lewis, PhD
Examiner
Art Unit 1623

James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

ptl
June 30, 2003